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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HIDEKI TOHDA, ET AL.	: EXAMINER: JOIKE, MICHELE, K.
SERIAL NO: 10/724,108	:
FILED: DECEMBER 1, 2003	: GROUP ART UNIT: 1636
FOR: METHOD OF CONSTRUCTING HOST AND METHOD OF PRODUCING HETEROLOGOUS PROTEIN	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

In accordance with 35 U.S.C. 134, that the claims of the present application have been twice rejected, this brief is submitted in response to the rejection dated January 26, 2009.

REAL PARTY OF INTEREST

The real party of interest herein is Asahi Glass Company, Ltd., Tokyo, Japan.

RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 14-15, 17-21 and 23-25 are active in this case.

Claims 14-15, 17-21 and 23-25 are rejected and appealed

STATUS OF AMENDMENTS

No outstanding amendments are present in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the pending, rejected and appealed independent claims 14 and 20 is outlined below with reference to exemplary support in the originally filed application.

14. A method of constructing a *Schizosaccharomyces pombe* yeast cell ***[page 6, lines 10-13]*** which produces a heterologous protein, ***[page 4, lines 9-16]*** comprising

deleting or inactivating at least one *S. pombe* gene encoding enzyme***[page 4, lines 9-16]*** selected from the group consisting of dipeptidyl aminopeptidase (SPAC14C4.15c), cytoplasmic aminopeptidase (SPAC13A11.05), -pyruvate decarboxylase pdc1 (SPAC1F8.07c), serine protease isp 6 (SPAC4A8.04), aminopeptidase (SPAC4F10.02), carboxypeptidase (SPBC16G5.09), carboxypeptidase (SPBC337.07c), vacuolar carboxylase S (SPAC24C9.08), zinc protease (SPACUNK4.12c), zinc protease SPCC1442.07c), metalloprotease (SPCC965.04c), zinc metalloprotease (SPAC17A5.04c), CAAX prenyl protease I ((SPAC3H1.05), dipeptidyl peptidase (SPBC1711.12), dipeptidase (SPCC965.12), methionine metallopeptidase (SPBC 14C8.03), methionine aminopeptidase (SPBC3E7.10), signal peptidase (SPAC1071.04c), and mitochondrial peptidase β subunit (SPBP23A10.15c); and ***[pages 10-21]***

transforming the *Schizosaccharomyces pombe* yeast cell with a polynucleotide which encodes the heterologous protein, ***[page 6, line 15-page 7, line 5]***

wherein the deletion or inactivation of the at least one gene results in increased production of the heterologous protein compared to a *Schizosaccharomyces pombe* yeast cell in which the at least one gene has not been deleted or inactivated. ***[page 8, lines 1-6]***

20. A method of producing a heterologous protein, comprising constructing a *Schizosaccharomyces pombe* yeast cell ***[page 6, lines 10-13]*** in which at least one *S. pombe*

gene is deleted or inactivated, ***[page 5, lines 2-11]*** wherein the at least one *S. pombe* gene encodes an enzyme selected from the group consisting of dipeptidyl aminopeptidase (SPAC14C4.15c), cytoplasmic aminopeptidase (SPAC13A11.05), pyruvate decarboxylase pdc1 (SPAC1F8.07), serine protease isp 6 (SPAC4A8.04), aminopeptidase (SPAC4F10.02), carboxypeptidase (SPBC16G5.09), carboxypeptidase (SPBC337.07c), vacuolar carboxylase S (SPAC24C9.08), zinc protease (SPACUNK4.12c), zinc protease (SPCC1442.07c), metalloprotease (SPCC965.04c), zinc metalloprotease (SPAC17A5.04c), CAAX prenyl protease I (SPAC3H1.05), dipeptidyl peptidase (SPBC1711.12), dipeptidase (SPCC965.12), methionine metallopeptidase (SPBC 14C8.03), methionine aminopeptidase (SPBC3E7.10), signal peptidase (SPAC1071.04c), and mitochondrial peptidase β subunit (SPBP23A10.15c); ***[pages 10-21]*** and

transforming the *Schizosaccharomyces pombe* yeast cell with a polynucleotide which encodes the heterologous protein, ***[page 6, line 15-page 7, line 5]***

wherein the deletion or inactivation of the at least one gene results in increased production of the heterologous protein compared to a *Schizosaccharomyces pombe* yeast cell in which the at least one gene has not been deleted or inactivated; ***[page 8, lines 1-6]***

culturing the yeast cell constructed such that the heterologous protein is produced by the yeast cell; and collecting the heterologous protein. ***[page 6, line 15-page 7, line 5]***

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole rejection to be reviewed on appeal is whether Claims 14-15, 17-21 and 23-25 are properly rejected under 35 U.S.C. 103(a) Egel-Matani (U.S. patent no 6,110,703) with the *S. pombe* database reportedly published on February 21, 2002 and Hombergh (Tibtech 15:256-263 (1997)).

ARGUMENT

The basis of the Examiner's rejection can best be understood by reference to the Official Action of August 6, 2008 because the final Official Action of January 26, 2009 to which this appeal is based indicates that the "rejection is maintained for reasons of record."

On page 5 of the Action of August 6, 2008, the Examiner asserts that the primary reference of Egel Matani teaches an method for the production of heterologous protein in a yeast which the Yap 3 protease has been deleted or whose activity has been reduced that results in an increased production of the polypeptide compared to the wildtype (unmodified)yeast.

The Examiner recognizes that Yap3 is not within the list of genes in the present claims.

The *S. pombe* database is relied upon to teach that the organism's genes were known as of February 21, 2002. (Action of August 6, 2008 bridging pages 5-6).

Reliance is also placed on the publication of Hombergh for teaching the improvement of heterlogous proteins in fungi.

Based on these combined teachings, the Examiner concludes that because (A) making a single gene deletion in a protease (Egel Matani) was known, (B) genes were known, and (C) making deletions and protein expression improvements in another unrelated fungi (Aspergillus from Hombergh), "it would have been obvious . . . to substitute one protease for another to achieve the predictable result of improving heterologous protein production." (Action of August 6, 2008 at page 6, last paragraph)

The invention as represented in the claims of this application are to a method of constructing a specific type of yeast cell *Schizosaccharomyces pombe* yeast cell which produces a heterologous protein or producing a heterologous protein in that specific type of cell, each of which delete a specific gene or genes.

The Office has the initial burden of proof to establish the prima facie obviousness of the subject matter Applicants claim in view of the prior art teaching. *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). Absent evidence which supports a rejection of the subject matter Applicants claim for obviousness, the Examiner's conclusion that Applicants' claims are unpatentable under 35 U.S.C. §103(a) must be withdrawn.

First, the Examiner appears to have ignored the fact that the prior art does not describe or reasonably suggest that the specific genes in the claims in the specific yeast strain, *S. pombe*. While Egel Matani teaches the results of a single gene in the same strain, the reliance for example of Hombergh to fill in the gaps of Egel Matani with the database overlooks a very important fact. Hombergh teaches Aspergillus, which while a Fungi is very different from *S. pombe* as defined in the claims. *S. pombe* is a type of unicellular yeast phylogenetically unrelated to Aspergillus, which is a filamentous fungi, e.g., molds and mildew.

Second, none of the cited references describe or otherwise suggest deleting or inactivating one or more specific genes, as recited in the claims, in *S. pombe* nor that by doing so, efficient production of heterologous proteins would result. Indeed, the prior art simply does not provide the expectation that experience in one cellular system would work nor work as well as it did for the applicants in another completely different system, *S. pombe* in the claims. Further, that Egel Matani had success with one particular gene encoding a protease and Hombergh's conclusions on a completely different type of organism simply does not provide a reasonably predictable result.

In establishing a prima facie case of obviousness, the cited references must be considered for the entirety of their teachings. Significantly, it is impermissible during

examination to pick and choose from a reference only so much that supports the alleged rejection. In this regard, it appears that it is only through hindsight reconstruction using Applicants' disclosure and selective picking and choosing that the Examiner attempts to reach the present invention through the cited combination of references. Hindsight reconstruction using only Applicants' disclosure to piece together cited references is, however, strictly prohibited. See M.P.E.P. § 2145. X.A.; see also *KSR International Co. v. Teleflex Inc.* , 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). (internal citations omitted) ("[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.")

Where, as here, the rejection of the subject matter Applicants claim is based on hindsight, the rejection is improper. *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Third, Conclusions of obviousness based on clearly erroneous findings, as is here the case, cannot stand. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 80 USPQ2d 1001 (Fed. Cir. 2006). The Examiner's conclusion of obviousness that teachings of a single gene and an unrelated organism can give rise to a predictable result must be erroneous. The conclusion of obviousness ignores the reality of experimentation in the field and the understood nature of differences in genomes, expression patterns, and other environmental influences. The conclusion ignores that S. pombe are uniquely different than Apergillus. The conclusion of obviousness ignores that protease genes, while sharing a name and generalized activity, say nothing to their role in the cellular metabolism, machinery and survival. And of further significance is that the conclusion of obviousness ignores the fact that the fields of cell biology and genetics are not as predictable as boldly stated in the rejection. "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely

to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd,* 533 F.3d 1353, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008).

Claims 15, 17, 21 and 23

With respect to Claims 15, 17, 21 and 23 Applicants argue separately, in addition to the reasons above, why the claims are patentable in view of the combined teachings of the cited art. Each of Claims 15, 7, 21 and 23 define a subset of genes in the claimed methods and as acknowledged in the Action at page 3, these genes are supported by the priority document to which the present application claims the benefit under 35 USC § 119.

The present application claims priority to PCT/JP02/05223 filed May 29, 2002 and JP2001-160128 filed May 28, 2001. Certified English translations of these documents were made of record. Therefore, in addition to the arguments submitted above with respect to all of the pending claims, separate consideration for these claims is requested based on Applicants' claim of benefit. That claim for benefit is before the February 21, 2002 date on which the cited *S. pombe* database was reportedly published.

CONCLUSION

Accordingly, in view of the above remarks and reasons explaining the patentable distinctness of the presently appealed claims over the prior art, Appellants request that the Examiner's rejection be REVERSED.

Respectfully submitted,

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APPENDIX 1 (CLAIMS)

Claims 1-13 (Cancelled)

14. (Rejected) A method of constructing a *Schizosaccharomyces pombe* yeast cell which produces a heterologous protein, comprising

deleting or inactivating at least one *S. pombe* gene encoding enzyme selected from the group consisting of dipeptidyl aminopeptidase (SPAC14C4.15c), cytoplasmic aminopeptidase (SPAC13A11.05), -pyruvate decarboxylase pdc1 (SPAC1F8.07c), serine protease isp 6 (SPAC4A8.04), aminopeptidase (SPAC4F10.02), carboxypeptidase (SPBC16G5.09), carboxypeptidase (SPBC337.07c), vacuolar carboxylase S (SPAC24C9.08), zinc protease (SPACUNK4.12c), zinc protease SPCC1442.07c), metalloprotease (SPCC965.04c), zinc metalloprotease (SPAC17A5.04c), CAAX prenyl protease I ((SPAC3H1.05), dipeptidyl peptidase (SPBC1711.12), dipeptidase (SPCC965.12), methionine metallopeptidase (SPBC 14C8.03), methionine aminopeptidase (SPBC3E7.10), signal peptidase (SPAC1071.04c), and mitochondrial peptidase β subunit (SPBP23A10.15c); and

transforming the *Schizosaccharomyces pombe* yeast cell with a polynucleotide which encodes the heterologous protein,

wherein the deletion or inactivation of the at least one gene results in increased production of the heterologous protein compared to a *Schizosaccharomyces pombe* yeast cell in which the at least one gene has not been deleted or inactivated.

15. (Rejected) The method of Claim 14, wherein the at least one enzyme is a pyruvate decarboxylase pdc 1 (SPAC1F8.07c).

16. (Cancelled).

17. (Rejected) The method of Claim 14, wherein the at least one enzyme is a serine protease isp 6 (SPAC4A8.04).

18. (Rejected) The method of Claim 14, wherein the at least one enzyme is an aminopeptidase (SPAC4F10.02).

19. (Rejected) The method of Claim 14, wherein the at least one enzyme is a carboxypeptidase (SPBC16G5.09).

20. (Rejected) A method of producing a heterologous protein, comprising constructing a *Schizosaccharomyces pombe* yeast cell in which at least one *S. pombe* gene is deleted or inactivated, wherein the at least one *S. pombe* gene encodes an enzyme selected from the group consisting of dipeptidyl aminopeptidase (SPAC14C4.15c), cytoplasmic aminopeptidase (SPAC13A11.05), pyruvate decarboxylase pdc1 (SPAC1F8.07), serine protease isp 6 (SPAC4A8.04), aminopeptidase (SPAC4F10.02), carboxypeptidase (SPBC16G5.09), carboxypeptidase (SPBC337.07c), vacuolar carboxylase S (SPAC24C9.08), zinc protease (SPACUNK4.12c), zinc protease (SPCC1442.07c), metalloprotease (SPCC965.04c), zinc metalloprotease (SPAC17A5.04c), CAAX prenyl protease I (SPAC3H1.05), dipeptidyl peptidase (SPBC1711.12), dipeptidase (SPCC965.12), methionine metallopeptidase (SPBC 14C8.03), methionine aminopeptidase (SPBC3E7.10), signal peptidase (SPAC1071.04c), and mitochondrial peptidase β subunit (SPBP23A10.15c); and

transforming the *Schizosaccharomyces pombe* yeast cell with a polynucleotide which encodes the heterologous protein,

wherein the deletion or inactivation of the at least one gene results in increased production of the heterologous protein compared to a *Schizosaccharomyces pombe* yeast cell in which the at least one gene has not been deleted or inactivated;

culturing the yeast cell constructed such that the heterologous protein is produced by the yeast cell; and collecting the heterologous protein.

21. (Rejected) The method of Claim 20, wherein the at least one enzyme is a pyruvate decarboxylase pdc 1 (SPAC1F8.07c).

22. (Cancelled).

23. (Rejected) The method of Claim 20, wherein the at least one enzyme is a serine protease isp 6 (SPAC4A8.04).

24. (Rejected) The method of Claim 20, wherein the at least one enzyme is an aminopeptidase (SPAC4F10.02).

25. (Rejected) The method of Claim 20, wherein the at least one enzyme is a carboxypeptidase (SPBC16G5.09).

APPENDIX II (EVIDENCE)

None

APPENDIX III

RELATED APPEALS AND INTERFERENCES

None.